monitor. J Extracorporeal Tech 19:322–329, 1987
4. Bashein G, Greydanus WK, Kenny MA: Evaluation of a blood gas and chemistry monitor for use during surgery. Anesthesiology 70:123–127, 1989
5. MIL-STD-810D: Environmental Test Methods and Engineering Guidelines, July 19, 1983
6. Hanlon JF: Handbook of Package Engineering. New York, NY, McGraw Hill, 1971
7. Harris C, Crede C: Shock and Vibration Handbook. New York, NY, McGraw Hill, 1961

MILITARY MEDICINE, 155, 11:527, 1990

Interactions between Nerve Agent Pretreatment and Drugs Commonly Used in Combat Anesthesia

LTC Jill R. Keeler, AN

Pyridostigmine is a drug stockpiled for oral pretreatment of nerve agent exposure; however, the soldier is still vulnerable to conventional warfare injuries, which are commonly associated with the need for anesthesia and surgery. In order to determine if we should be concerned about pyridostigmine-drug interactions, a comprehensive search of existing literature on pyridostigmine and selected drugs contained in the Defense Medical Standardization Board D-Day Items list was completed. It appears that the most significant interaction might be with the neuromuscular blocking drugs used in anesthesia, which in turn could pose the greatest casualty management concerns. Other potential interactions are discussed, along with a review of the pharmacology of pyridostigmine.

Introduction

In response to an increasingly important threat of chemical warfare, the United States military employs a treatment regimen that consists of atropine and pralidoxime (2-PAM) by autoinjector upon exposure to nerve agent. Oral pyridostigmine (PYR) has now been added to the regimen as a pretreatment compound. Proper administration of this drug combination increases the probability of survival even after otherwise lethal exposures to nerve agents.

When a high threat of exposure to nerve agent has been determined to exist, soldiers are given a blister pack containing 21 PYR 30 mg tablets and instructed to take one tablet every 8 hours. Continuation of the pretreatment regimen is normally reassessed every 3 days based on advice from chemical/medical/intelligence staff officers, but continuance beyond 2 weeks is discouraged.

It must be stressed that PYR administration alone will not protect a soldier from the lethal effects of nerve agent. Upon exposure, the soldier must immediately administer the atropine/2-PAM antidote. This combination of drugs (PYR, atropine/2-PAM), administered appropriately, enhances the likelihood that the casualty will continue to breathe spontaneously and not die due to ventilatory arrest.

A chemical threat does not preclude a soldier from being wounded with conventional weapons. Thus, there may be many PYR-treated soldiers on the battlefield, even though exposure to nerve agent may not occur. The wounded casualty is likely to require anesthesia and surgery and therefore encounter drugs at field medical units, such as analgesics, anesthetics, and antibiotics. Clinicians must consider the possibilities of PYR-drug interactions in managing these patients. Very few studies or reports identify specific interactions, but with a good understanding of the pharmacology of PYR, potential problems can be avoided. This report provides a review of the pharmacology of PYR as well as some caveats for clinicians involved in perioperative care.

Pharmacology of Pyridostigmine

Chemistry

PYR is a dimethylcarbamate containing a quaternary amine moiety (Fig. 1). Due to the quaternary amine, it does not readily penetrate the blood-brain barrier, and its effects and interactions should therefore be peripheral. However, in the event of overdose there is evidence that it might penetrate that barrier, e.g., psychoses due to cholinergic toxicity in patients with myasthenia gravis taking neostigmine (another dimethylcarbamate with quaternary amine) have been reported.[1]

Pharmacokinetics

There is no significant plasma protein binding,[2] which implies that there are no drug interactions involving competition for protein binding sites. Of the absorbed dose, 75% to 90% is excreted in the urine unchanged,[2,3] and the remainder is metabolized. At the proposed dosage regimen, acetylcholinesterase (AChE) levels return to normal 12 hours after the last dose.[4]

From the Physiology Branch, Pathophysiology Division, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Grounds, MD.

This manuscript was received for review in June 1989. The revised manuscript was accepted for publication in February 1990.

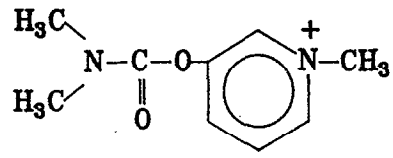

Fig. 1. Pyridostigmine

Mechanism of Pretreatment Against Nerve Agents

Both PYR and nerve agents are anticholinesterases, the major difference being that nerve agents bind irreversibly and PYR binds reversibly to the enzyme AChE. Many toxic effects of nerve agents are due to the inhibition of AChE, allowing acetylcholine (ACh) to build up at crucial cholinergic synapses because of depressed catabolic activity. The prescribed dose of PYR results in about 30% reversible inhibition of AChE, leaving 70% of the enzyme unprotected and subject to irreversible inhibition by nerve agent.

Effects

In addition to the inhibition of AChE, which leads to the accumulation of ACh, PYR also has direct cholinergic agonist effects.[5,6] Its major effects are, therefore, a result of muscarinic and nicotinic ACh receptor activation. Drug interactions with PYR involve interactions at muscarinic or nicotinic receptors, or can be the result of inhibited enzyme per se.

Activation of peripheral muscarinic receptors affects several organ systems and causes gastrointestinal hypermotility, cramping, nausea, vomiting, diarrhea, salivation, lacrimation, urination, sweating, increased tracheobronchial secretions, bronchoconstriction, miosis, bradycardia, and atrioventricular conduction slowing. Effects of nicotinic receptor activation are involved largely at the neuromuscular junction and include muscle cramps, fasciculations, and weakness.

At the dosage recommended in AHS Field Circular 8-48 (26 March 1987), rare side effects include a slight increase in flatus, occasional looseness of the bowels, and a decrease in heart rate of about 5 beats per minute.[7] Nevertheless, if another drug with cholinergic properties is administered in "normal" dosages to a PYR-treated casualty, the two may be additive and the more severe physiologic effects of muscarinic receptor activation will occur. Similarly, if it is necessary to give the PYR-treated casualty an anticholinergic, e.g., to increase heart rate, a larger dose may be needed to get the desired effect.

Selected Drugs Available in Field Medical Facilities and Potential Interactions with Pyridostigmine Where Applicable

The following listing of possible PYR-drug interactions is based on (1) similar target sites at either the ACh receptor or AChE, (2) interference with the metabolism of drugs, (3) availability of drugs in the field environment, and (4) the likelihood of a casualty to receive the drugs. The examples listed are actual drugs included in the Defense Medical Standardization Board (DMSB) and Deployable Medical Systems (DEPMEDS) D-Day Item lists. An asterisk (*) indicates inclusion in the DMSB but not the DEPMEDS list. The premedicants are cimetidine (Tagamet), hydroxyzine (Vistaril), and promethazine (Phenergan). Diazepam, morphine, etc., will be addressed later.

It is unlikely that the above premedicants will be administered in a combat setting, because most of the surgery performed will be emergency trauma surgery. However, in the event semi-elective surgery is performed, or in the mass casualty situation when the patient is triaged, there may be enough time to administer premedicants.

Cimetidine is a histamine-2 receptor blocker that is sometimes administered about an hour prior to anesthesia in order to raise the pH of gastric secretion.[8] Because all traumatic casualties are assumed to have full stomachs and are therefore at risk for aspiration of stomach contents, it is desirable to ensure that the risk of aspiration pneumonitis is minimized. The specificity of cimetidine for the histamine-2 receptor suggests no interactions with PYR.

Hydroxyzine may be used preoperatively as an anxiolytic, as an antiemetic, and as an opioid potentiator. It also has antihistaminic (H1) properties.[9] Another H1 blocker (diphenhydramine) has been reported to have antinicotinic activity[10] and in fact reverses organophosphate-induced neuromuscular blockade.[11] Hydroxyzine has not been reported to share the antinicotinic actions, so interactions with PYR are doubtful.

Promethazine, a phenothiazine, is used at times as a premedicant to exploit its sedative, antihistaminic, anticholinergic, and antiemetic properties.[12] The peripheral interaction with PYR at muscarinic receptors should offset the anticholinergic effects of promethazine and be of little significance. There have been isolated reports of prolonged apnea from other phenothiazines in combination with a variety of cholinomimetic drugs, including succinylcholine and organophosphorus compounds, which can result in a prolonged neuromuscular block. Apparently phenothiazines also inhibit cholinesterases.[13,14] Theoretically, a PYR-treated patient could get a summation of three ACh effects if administered promethazine and succinylcholine.

Antimuscarinics: Atropine, Glycopyrrolate (Robinul), Scopolamine

These drugs are commonly used in anesthesia to decrease oral secretions, to protect against vagal reflexes that can result in laryngospasm, and to protect against and/or treat bradyarrhythmias.[15] Many of the undesirable effects of PYR originate at muscarinic receptors, and an antimuscarinic is the drug of choice for PYR overdose.[16] Because PYR and antimuscarinics have antagonistic actions, a casualty with therapeutic levels of PYR in his system will require larger than normal doses of antimuscarinics.

Intravenous Anesthetics

There should be little if any interaction between PYR and IV anesthetics since IV anesthetics' major sites of action are in the central nervous system (CNS), and PYR works peripherally. In some cases, however, IV anesthetics also have peripheral effects. These peripheral effects may originate in the CNS or may be a result of a direct action on a particular organ or organ system. The potential peripheral drug interactions are discussed.

Barbiturates: Sodium Thiopental (Pentothal)

Thiopental is a very popular drug used to induce general anesthesia. A relative contraindication to the use of thiopental

is in individuals who have asthma. Under light levels of anesthesia, thiopental can precipitate bronchospasm in susceptible individuals.[9] PYR is also contraindicated in asthmatics for the same reason. Therefore, thiopental should be used with caution in PYR-treated casualties.

Thiopental occasionally causes "excitatory phenomena" under light levels of anesthesia, which may present as spontaneous tremor, hypertonus, cough, hiccough, or laryngospasm.[17] The latter three symptoms are largely a result of vagal (ACh) activity; therefore, thiopental should be avoided in PYR-treated casualties when alternative induction agents are available. If thiopental is the only available induction agent, it should be preceded with an adequate dose of antimuscarinic.

Finally, thiopental causes a fall in cardiac index, stroke volume, and blood pressure.[17] PYR can cause bradycardia with a consequent fall in cardiac output and blood pressure.[18] Thiopental should be used with caution in "shocky" casualties regardless of the etiology, and in soldiers with myocardial ischemic disease. Pretreated patients may be at increased risk because of additive effects.

Benzodiazepines: Diazepam (Valium)

Diazepam has very little peripheral effect; therefore, interactions with PYR should be minimal. Caution should be used if diazepam is given as an induction agent in a PYR-treated shocky casualty, since the minimal cardiovascular depressant effects[9] of diazepam might be accentuated.

Butyrophenones: Droperidol (Inapsine)

Droperidol is used in combination with opioids to produce "neuroleptanalgesia." It is also used alone to prevent/treat vomiting associated with anesthesia and surgery. These central effects are due to dopamine competitive antagonism. Droperidol also acts peripherally and can cause hypotension via alpha-adrenergic blockade. PYR interactions would not be expected.

Arylcyclohexylamines: Ketamine (Ketalar)

Ketamine produces "dissociative anesthesia," characterized by a bizarre trance-like state in which the patient appears to be dissociated from his environment. Ketamine is considered a good induction agent for combat/trauma casualties because it supports the cardiovascular system.[19,20] Ketamine increases heart rate, contractility, cardiac output, and blood pressure by interacting with the sympathetic nervous system, and should therefore tend to offset the negative effects of PYR. Ketamine also causes bronchodilation that offsets PYR's potential constrictive effects on bronchial smooth muscle.

Two words of caution: (1) Both PYR and ketamine increase the production of oropharyngeal secretions. Ketamine leaves laryngeal reflexes intact and may in fact sensitize them to stimuli; the secretions then could trigger a laryngospasm. The risk of laryngospasm can be minimized with an adequate dose of antimuscarinic prior to the administration of ketamine. (2) The elimination half-life for ketamine is about 3 hours; however, it is biotransformed to several active metabolites, which may account for the prolonged psychic side effects. Rapid return to duty within 24 hours may not be feasible, depending on the tasks and responsibilities peculiar to the duty position of the serviceman.

Finally, there is mounting evidence that ketamine interacts directly with AChE. Ketamine protects AChE against sarin inhibition in vitro; however, the in vivo significance is yet to be determined.[21]

Opioids: Fentanyl (Sublimaze), Meperidine (Demerol), Morphine, Nalbuphine (Nubain), Naloxone (Narcan)

Morphine and meperidine will be administered to battlefield casualties for analgesia. Fentanyl will be used to provide analgesia intraoperatively as a component of "balanced anesthesia." Naloxone, an opioid antagonist, may be used to reverse the adverse effects of balanced anesthesia due to opioids, e.g., ventilatory depression. Nalbuphine is an opioid "partial agonist" with some sedative effects and not as potent as the aforementioned agonists, so it will be used in situations in which a less potent opioid is needed, such as adjunct to regional anesthesia. It may also be used to reverse effects of the full agonists.

Opioids are so named because they interact specifically with opioid receptors; therefore, cholinergic receptor crossover is not a problem. However, selected organ systems do contain both opioid and cholinergic receptors, so physiologic outcome may be affected.

Centrally mediated effects of opioids include analgesia, ventilatory depression, miosis, and vomiting. The major peripheral site of action is the gastrointestinal tract and the major effect is constipation.

Of little clinical significance is the opposite effects of PYR and opioids on the gastrointestinal tract. An opioid would likely negate complaints of increased flatus and loose bowels, though that is the least of the casualty's worries at this time.

Morphine causes arteriolar and venous dilation (partially via histamine release), and orthostatic hypotension may be accentuated in the presence of PYR. Fentanyl, like PYR, occasionally causes bradycardia that can be treated with an antimuscarinic. Meperidine, on the other hand, often results in tachycardia (it was originally synthesized 50 years ago to be an atropine-like agent), and this intrinsic pharmacologic property may counteract any PYR-induced bradycardia and possibly make it a better choice of analgesic.

A possible interaction between meperidine and PYR exists because meperidine is an ester and is hydrolyzed by liver enzymes to meperidinic acid. Apparently anticholinesterases (and presumably PYR) do not inhibit these esterases. A pharmacokinetic study indicated no differences in plasma elimination half-lives of meperidine in guinea pigs subjected to a 90% LD50 dose of soman or placebo, 1 or 12 hours before meperidine.[22]

A minor perplexing situation might arise if an opioid is used in balanced anesthesia: the anesthetist uses pupillary size as one indicator of depth of opioid anesthesia. Although the PYR-pretreatment regimen does not cause miosis, it is not known whether the pupils are at least resistant to dilation. This could be confusing to the anesthetist, particularly at the end of a case when assessing reversal criteria, i.e., whether or not to administer naloxone or nalbuphine if the patient is too "sleepy," even with adequate ventilatory excursion. Of course, all this may be a moot point because the patient will probably be atropinized from the start of the anesthetic.

Neuromuscular Blockers: Pancuronium Bromide (Pavulon), Succinylcholine (Anectine, Quelicin, Sucostrin, Sux-Cert)

Neuromuscular blockers (NMBs) are used in anesthesia (1) to facilitate endotracheal intubation and (2) for surgical relaxation. Their major site of action is the nicotinic receptor at the muscle membrane of the neuromuscular junction (NMJ).

Nondepolarizing NMBs (e.g., pancuronium bromide) are competitive antagonists for ACh and prevent the binding of ACh to its receptors, but produce no direct effect themselves. Pancuronium is a long-acting NMB (duration 45–60 minutes), with cumulative dose effects. Theoretically, since PYR may increase the concentration of ACh at the NMJ, more nondepolarizing NMB will be needed to get the desired muscle relaxation. In fact, a major clinical use of PYR is to reverse the neuromuscular effects of NMBs used in anesthesia. These antagonistic effects have been well documented,[23,24] and the fact that pancuronium itself inhibits plasma AChE makes it even more difficult to achieve desired block.[25,26]

In contrast, depolarizing NMBs (e.g., succinylcholine, "SCh") are ACh agonists. This type of blockade is the type that occurs from exposure to organophosphorus compounds. The binding of depolarizing NMBs to receptor sites at the muscle membrane causes a depolarization that persists longer than that caused by ACh, because AChE does not hydrolyze SCh. A second action potential cannot occur as long as the membrane is still depolarized, hence paralysis, or "phase I" blockade. Since PYR treatment may also provide more agonist at the NMJ, less SCh should be needed to achieve phase I block. PYR and SCh have potentiating effects via another mechanism as well: SCh is rapidly metabolized principally by "pseudocholinesterase" or plasma cholinesterase. This rapid metabolism is the reason for SCh's short duration of action. PYR is a nonspecific anticholinesterase. It inhibits AChE found in the membranes of red blood cells and at all cholinergic synapses, and also pseudocholinesterase found in the plasma, liver, kidney, and intestines. Therefore, PYR may prolong the action of SCh by inhibiting its metabolism. Indeed, any drug that inhibits pseudocholinesterase will prolong the action of SCh.[27,28] The clinical significance of this is yet to be determined, because a 75% to 80% decrease in levels of the normal enzyme is necessary for a significant increase in neuromuscular block following SCh.[29]

Finally, overdose of ACh agonist at the NMJ (which may be possible with PYR + SCh) can result in "phase II" or "desensitization" neuromuscular blockade. This is known to occur with continuous SCh drip or repeated intermittent boluses, and the likelihood of it occurring increases with concomitant anticholinesterase. This type of block induced by PYR + SCh has been reported.[30,31] Although the underlying mechanism(s) is complex, the type of block exhibits many of the classic characteristics of a nondepolarizing block, demonstrated clinically with a peripheral nerve stimulator. Like a nondepolarizing block, an advanced phase II block can be reversed with an anticholinesterase.[32,33] For a more in-depth discussion of phase I and phase II blocks, see Churchill-Davidson et al.[34] and Lee.[35]

The conclusion on PYR/NMB interactions is this: antagonism or potentiation of NMBs is likely to occur. The best way to assess cholinergic status at the NMJ and, hence, NMB dose is by careful monitoring with a peripheral nerve stimulator. Although experienced anesthetists can often correctly assess the cholinergic status at the NMJ without a peripheral nerve stimulator, blind attempts to do this in a PYR-treated casualty is likely to result in many cases of prolonged apnea.

Anticholinesterases: Edrophonium (Tensilon), Neostigmine (Prostigmin)

Anticholinesterases are used routinely in anesthesia to "reverse" neuromuscular block induced by nondepolarizing NMBs. Inhibition of AChE allows ACh to accumulate and competitively overwhelm nondepolarizing NMBs at ACh receptors. Although the intent is to allow accumulation of ACh at the NMJ, accumulation at muscarinic receptors dictates that an antimuscarinic be administered concurrently. These drugs (edrophonium and neostigmine) share the same mechanism of action as PYR at the NMJ, and in fact, PYR is used for this purpose at medical treatment facilities during peacetime (i.e., PYR is not included in the DMSB/DEPMEDS D-Day Item list in the injectable formulation).

Although more nondepolarizing NMB is needed to achieve the desired level of muscle relaxation in a PYR-treated individual in order to compete for ACh binding sites, reversal of the block should be initiated with a "normal" dose of anticholinesterase, since the ratio of NMB:ACh is about the same as in an untreated patient. Again, meticulous monitoring with a peripheral nerve stimulator is indicated.

Occasionally, an anticholinesterase might be administered during anesthesia to treat paroxysmal atrial tachycardia (PAT).[36] The additive effects of this treatment for PAT in a PYR-treated patient should be kept in mind.

Inhalation Agents: Enflurane (Ethrane), Halothane (Fluothane), Isoflurane (Forane), Nitrous Oxide

These drugs are used for maintenance of general anesthesia and hence most of their actions are in the CNS.

A potentially beneficial effect of the use of inhalation anesthetics in a PYR-treated patient is their effect on bronchial smooth muscle. Many inhalation anesthetics have a direct bronchodilating effect, which might offset the negative effects of PYR or PYR + thiopental at this site.

The halogenated inhalation anesthetics also cause skeletal muscle relaxation with the clinical characteristics of nondepolarizing type blockade; they also potentiate nondepolarizing muscle relaxants. Their neuromuscular blocking potency is: enflurane = isoflurane >> halothane > control.[37–39] The use of isoflurane or enflurane in PYR-treated patients might be advantageous, since it would obviate the need for increased doses of nondepolarizing NMBs.

SCh is also potentiated by isoflurane > enflurane = halothane.[37,40] Use of isoflurane in a PYR-treated patient should therefore further decrease the requirement for SCh.

Nitrous oxide: no interactions with PYR are expected.

Local Anesthetics (LAs): Bupivacaine (Marcaine), Cocaine, Lidocaine (Xylocaine), Tetracaine (Pontocaine), Mepivacaine (Carbocaine)

Regional anesthesia is generally not practical for combat casualties because it takes more time to administer, and the extent of multiple traumatic injuries often extends beyond what a regional anesthetic can cover.

Of the LAs available, potential drug interactions with PYR exist for the esters, because ester LAs are hydrolyzed princi-

pally by plasma cholinesterase. PYR inhibits this enzyme, so it should prolong the action of ester LAs, but more importantly it would increase serum levels of these drugs, which could lead to central nervous system and cardiovascular toxicity. The only ester LAs available in the DMSB/DEPMEDS D-Day Item lists are cocaine and tetracaine.

Tetracaine can be used for subarachnoid block or brachial plexus block. The highest dose used for subarachnoid block is about 20% of the maximum suggested therapeutic dose, so there is a large margin of safety. However, when tetracaine is incorporated in a brachial plexus block, the highest doses used approach the maximum suggested therapeutic dose. Inhibition of tetracaine's metabolism, even to a small degree by PYR, could result in seizures and cardiorespiratory depression.

Cocaine is used as a topical anesthetic for the mouth, nose, and throat. Besides its LA properties, cocaine markedly inhibits reuptake of catecholamines from nerve terminals (the major way catecholamine effects are terminated). Cocaine therefore potentiates physiologic responses to catecholamines, most notably involving the cardiovascular system. In addition to hydrolysis by plasma cholinesterase, to a lesser extent metabolism/elimination is via liver enzymes and some is excreted unchanged. With AChE inhibition, there is no compensatory increase in liver metabolism or renal excretion of the parent compound,[41] and serum levels necessarily rise. Since maximum safe doses are frequently administered, toxicity could easily ensue in the form of acute hypertension and dangerous ventricular dysrhythmias. This could be even more serious if a halogenated inhalation agent were added to the anesthetic regimen since this type can sensitize the myocardium to catecholamine-induced dysrhythmias.

Because of these potential adverse effects and the availability of amide LAs that are efficacious for brachial plexus blocks and topical anesthesia, the esters are not recommended.

Miscellaneous: Dantrolene (Dantrium), Doxapram (Dopram) (Dopram)

These drugs are also used in the perioperative period, but do not fall nicely into the above categories.

Dantrolene is the only drug shown to be an effective pretreatment/treatment for the pharmacogenetic disorder malignant hyperthermia, a life-threatening consequence of anesthesia; the incidence in the general hospital population is 1:50,000.[42] Certain drugs associated with anesthesia (e.g., SCh and halothane) are known triggers of this hypermetabolic syndrome characterized by an increase in any or all of the following: end-tidal CO_2 concentration and $PaCO_2$, lactic acid production, O_2 consumption, serum potassium, body temperature, muscular rigidity, dysrhythmias, tachypnea, and a mixed acidosis.[43] While the complete mechanism as to dantrolene's effectiveness is not known, the drug inhibits calcium release from the sarcoplasmic reticulum. Since PYR acts at the NMJ and dantrolene acts directly on the muscle, there are not expected to be any interactions. If in this case one can generalize to anticholinesterases, soman increases calcium pump activity,[44] which should enhance the effects of dantrolene. PYR is not a known trigger agent of malignant hyperthermia.

Doxapram is sometimes used postoperatively to stimulate ventilation via an action on peripheral and central chemoreceptors. PYR should not interact with this drug.

Antibiotics: Neomycin, Gentamicin, Tetracycline, Clindamycin, Metronidazol

There are more antibiotics listed in the DMSB/DEPMEDS D-Day Item lists than these; however, these drugs inhibit ACh release at the NMJ, have postjunctional effects, and are known to potentiate the block of nondepolarizing NMBs.[45] In a PYR-treated individual, this side effect may be negated.

Hemorrhage and Nerve Agent Pretreatment/ Treatment Drugs: Implications for Anesthesia and Surgery

Hemorrhage is addressed in this report to complete the potential PYR interactions in the perioperative period.

Multiple trauma is common in conventional warfare injuries. As a result, hemorrhagic hypovolemia is common and may present additional difficulties in patients who are pretreated or treated for exposure to nerve agent. Wade et al.[46–49] used a conscious pig model to investigate the effects of hemorrhage on AChE (red blood cell [RBC] and plasma) levels, acute PYR treatment (to possibly simulate nerve agent), chronic PYR pretreatment, atropine treatment, and 2-PAM treatment. They monitored heart rate, blood pressure, arterial blood gases, blood lactate and glucose, hematocrit, RBC, and plasma AChE. Hemorrhage to 50% of the estimated blood volume caused a similar reduction in blood pressure and hematocrit in all groups as well as a 15% to 18% decrease in plasma AChE activity, but no change in RBC AChE.

PYR pretreatment for 3 days decreased plasma AChE by 37% and RBC AChE by 35%, but had little effect on changing the course of the physiologic response to hemorrhage. Even though 75% of absorbed PYR is eliminated unchanged in the urine and 25% metabolized in the liver, the hemorrhage and presumed fall in renal and hepatic blood flow did not prolong the elimination of PYR.

In atropine and 2-PAM treated pigs there were no significant differences in physiologic and metabolic variables between hemorrhage-control and hemorrhage-treated groups.

In summary, it does not appear that the pathophysiologic effects of hemorrhagic hypovolemia will be worsened by the current therapeutic countermeasures to nerve agents.

Significance of Inhibition of Cholinesterase: Acute versus Chronic Therapy

It has been demonstrated in several receptor systems including the ACh receptor system[50] that with continued agonist input the bombarded receptors become desensitized or down-regulated. Subjects become tolerant to the effects of agonists and sensitive to the effects of antagonists. This process takes time and results in either an increase in nonconducting receptor conformations or an actual decrease in the number of receptors. The topic of tolerance to anticholinesterases (organophosphorus compounds and carbamates) is reviewed at length by Costa et al.[51]

In a PYR-treated individual, receptors are constantly being bombarded by excess ACh (as well as by PYR agonist activity). Would desensitization occur under the pretreatment regimen prescribed by doctrine? There is in vitro electrophysiologic evidence that PYR can cause nicotinic receptor desensitization

at the neuromuscular junction.[52] Two separate in vivo studies further support this notion: rats received PYR chronically for up to 14 and 20 days, and showed a dose- and frequency-dependent decrease in skeletal muscle contractile force in response to tetanic stimulation of the appropriate nerve. This phenomenon occurred as early as the first day of treatment and persisted as long as 20 days. There were no changes in nerve function per se.[53,54] These results suggest the possibility of desensitization of acetylcholine receptors at the NMJ.

If down-regulation of ACh receptors occurs in soldiers taking the prescribed pretreatment regimen, many of the drug interactions previously described could have directly opposite effects. The most significant consequences would be with NMBs. In a down-regulated receptor scenario, ACh receptors would be resistant to the effects of agonists. More SCh would be needed to establish sufficient relaxation for intubation. ACh receptors would be sensitive to the effects of competitive antagonists. Less pancuronium would be needed to attain adequate surgical relaxation, and conventional doses would lead to prolonged apnea, especially since this drug has an inherent extended duration of action.

It is difficult to estimate if and when down-regulation would occur in PYR-treated patients. Not knowing if and when down-regulation occurs could result in an inordinate number of ventilatory-depressed patients. The best way to avoid multiple casualties with long-term need for mechanical ventilation is to monitor neuromuscular function with a peripheral nerve stimulator. It may even be possible to determine at the onset of anesthesia, with a peripheral nerve stimulator, the "condition" of ACh receptors and then administer NMBs accordingly. For example, a defasciculating/test dose of pancuronium is given, and there is evidence of "significant" nondepolarizing blockade as determined by the peripheral nerve stimulator. This tells the anesthetist that, in order to achieve muscle relaxation for intubating conditions in a timely manner, down-regulation has occurred and a higher dose of SCh is needed. A clinical study may be indicated to determine whether such a test is possible.

Discussion

In the event of a future conflict, preparedness for chemical warfare is an absolute requirement. Fortunately, U.S. forces are likely to survive a nerve agent attack because of the addition of oral PYR pretreatment to the atropine/2-PAM regimen. Our pretreated troops, however, are still subject to wounds by conventional weapons, which most often necessitate anesthesia and surgery.

A good understanding of the pharmacology of PYR and other drugs available in the field medical units dictates careful titration-to-effect (when possible) of all drugs. This alone may be enough to minimize potential drug interactions.

Because many potential interactions may lead to overstimulation of muscarinic receptors and hence unwanted effects (e.g., laryngospasm, bradycardia), it follows that all PYR-treated patients should be adequately atropinized prior to the induction of anesthesia. Furthermore, these patients may need additional atropine intraoperatively.

The overwhelming likelihood of a drug interaction is with the neuromuscular blockers. The only way available to avoid the possibility of extended ventilatory insufficiency due to paralysis by these drugs is through careful monitoring of neuromuscular function. A peripheral nerve stimulator should therefore be available for every general anesthetic. Appropriate information channels should be used to alert the potential combat anesthesia providers of the need for use of these monitors.

Addition (or substitution) of a nondepolarizing neuromuscular blocker of shorter duration for pancuronium bromide in the DMSB/DEPMEDS D-Day Item lists may also be warranted. Vecuronium bromide is an intermediate-acting (duration of 15 to 30 minutes) nondepolarizing neuromuscular blocker without cumulative effects as well as being pharmacologically reversible, so extended periods of apnea should be minimized in the event of interaction-related overdose. Vecuronium bromide has also been used in lieu of the depolarizing neuromuscular blocker, succinylcholine, when rapid intubation conditions might be necessary.[55,56] Furthermore, a drug such as vecuronium that is supplied as a freeze-dried formulation that can be stored at room temperature is superior, in the combat field or warehouse footlocker scenario, to drugs that should be refrigerated (e.g., pancuronium and succinylcholine).

Finally, the possible effect of desensitization at the neuromuscular junction and concurrent adverse potentiation of neuromuscular blockers may be an issue that deserves further review. It should be determined what the effects are (if any) of chronic administration (1 to 4 weeks) of pyridostigmine on human neuromuscular function. It may even be possible to observe changes (if present) using the peripheral nerve stimulator. If a human study is not feasible, then worst-case scenarios should be considered and drugs administered accordingly. For example, succinylcholine will initially be administered at 1.5 times the normal dosage to facilitate endotracheal intubation, and pancuronium will initially be administered at 0.5 times the normal dosage to provide surgical relaxation; subsequent doses will be injected based on information provided by the peripheral nerve stimulator. Again, addition of a drug such as vecuronium to the combat anesthesia armamentarium may obviate such considerations: its enhanced potency in a desensitized individual would better facilitate rapid intubation, and this initial intubating dose might well be sufficient for surgical relaxation to the end of the procedure.

The preceding theoretical analyses of possible drug interactions will likely require revisions, as further experimental results and possible practical experiences reveal aspects as yet not foreseen.

References

1. Abel VM, Kohlmeyer K: Uber das cholinergisch-toxische Psychosyndrom prostigminbehandelter Myastheniker. Dtsch Med Wschr 91:699–703. 1966
2. Kornfeld P, Samuels AJ, Wolf RL, et al: Metabolism of 14C-labeled pyridostigmine in myasthenia gravis. Neurology 20:634–641, 1970
3. Cronnelly R, Stanski DR, Miller RD, et al: Pharmacokinetics of pyridostigmine in patients with and without renal function. Clin Pharmacol Ther 28:78–81, 1980
4. Moylan-Jones RJ, Parkes DC, Sellers RP, et al: The pharmacokinetics of pyridostigmine in humans Part II. Multiple dose studies. CDE Tech Paper #258, March 1979
5. Gallagher JP, Wong L, Hasuo H: Effects of pyridostigmine on spontaneous and synaptic activity recorded intracellularly, *in vitro*, from rat dorsolateral septal nucleus. Proc Med Chem Def Biosci Rev 6:507–510,

1987
6. Shinnick-Gallagher P: Effect of pyridostigmine at muscarinic, adrenergic and purinergic sites in mammalian parasympathetic ganglia. Proc Med Chem Def Biosci Rev 6:479–482, 1987
7. Gall E: The use of therapeutic mixtures in the treatment of cholinesterase inhibition. Fund Appl Toxicol 1:214–216, 1981
8. Stoelting RK: Psychological preparation and preoperative medication. In: Anesthesia Vol. 1, Edited by Miller RD, New York: Churchill-Livingstone, 1981, pp 101–103
9. AMA-DE (AMA Drug Evaluations), 4th ed., 1980
10. Hernandez L: Estudio sobre el mecanismo de accion de la difenhidramina como antidoto en intoxicaciones por organofosforados. Acta Medica Valle 4:101–104, 1973
11. Clemmons RM: Meyer DJ, Sundlof SF, et al: Correction of organophosphate-induced neuromuscular blockade by diphenhydramine. Am J Vet Res 45:2167–2169, 1984
12. Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: The Pharmacological Basis of Therapeutics, Edited by Gilman AG, Goodman LS, Gilman A. New York: Macmillan, 1980, p 627
13. Regan AG, Aldrete JA: Prolonged apnea after administration of promazine hydrochloride following succinylcholine infusion. Anesth Analg 46:315–318, 1967
14. Arterberry JD, Bonifaci RW, Nash EW, et al: Potentiation of phosphorus insecticides by phenothiazine derivatives. JAMA 182:848, 1962
15. Wood M: Anticholinergic drugs; anesthetic premedication. In: Drugs and Anesthesia, Edited by Wood M, Wood AJJ. Baltimore: Williams & Wilkins, 1985a, pp 141–162
16. Wood M: Cholinergic and parasympathomimetic drugs. Cholinesterases and anticholinesterases. In: Drugs and Anesthesia, Edited by Wood M, Wood AJJ. Baltimore: Williams & Wilkins, 1985b, pp 111–140
17. Wood M: Intravenous anesthetic agents. In: Drugs and Anesthesia, Edited by Wood M, Wood AJJ. Baltimore: Williams & Wilkins, 1985c, pp 199–239
18. Arsura EL, Brunner NG, Namba T, et al: Adverse cardiovascular effects of anticholinesterase medications. Am J Med Sci 293:18–23, 1987
19. Lenz G, Stehle R: Anesthesia under field conditions: a review of 945 cases. Acta Anaesthesiol Scand 28:351–356, 1984
20. Sherner JH: Combat anesthesia. Emerg Care Q 2:30–36, 1987
21. Puu G: Ketamine protects acetylcholinesterase against *in vitro* inhibition by sarin. Biochem Pharmacol 37:969–970, 1988
22. Castle MC: Alteration of the efficacy and toxicity of clinically useful drug esters by OP inhibitors. Q Rep #DAMD17-84-C-4120, Jan-Mar, 1987
23. McNall PG, Wolfson B, Tuazon JG, et al: Use of pyridostigmine for the reversal of neuromuscular blockade. Anesth Analg 48:1026–1032, 1969
24. Fogdall RP, Miller RD: Antagonism of d-tubocurarine- and pancuronium-induced neuromuscular blockades by pyridostigmine in man. Anesthesiology 39:504–509, 1973
25. Stovner J, Oftedal N, Holmboe J: The inhibition of cholinesterases by pancuronium. Br J Anaesth 47:949–954, 1975
26. Mirakhur RK, Ferres CJ, Lavery TD: Plasma cholinesterase levels following pancuronium and vecuronium. Acta Anaesthesiol Scand 27:451–453, 1983
27. Pantuck EJ: Echothiophate iodide eye drops and prolonged response to suxamethonium. Br J Anaesth 38:406–407, 1966
28. Gesztes T: Prolonged apnoea after suxamethonium injection associated with eye drops containing an anticholinesterase agent. Br J Anaesth 38:408–409, 1966
29. Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with genotypically normal enzyme. Anesthesiology 53:517–520, 1980
30. Bentz EW, Stoelting, RK: Prolonged response to succinylcholine following pancuronium reversal with pyridostigmine. Anesthesiology 44:258–260, 1976
31. Bishop MJ, Hornbein TF: Prolonged effect of succinylcholine after neostigmine and pyridostigmine administration in patients with renal failure. Anesthesiology 58:384–386, 1983
32. Donati F, Bevan DR: Antagonism of phase II succinylcholine block by neostigmine. Anesth Analg 64:773–776, 1985
33. Futter ME, Donati F, Sadikot AS, et al: Neostigmine antagonism of succinylcholine phase II block: a comparison with pancuronium. Can Anaesth Soc J 30:575–580, 1983
34. Churchill-Davidson HC, Christie TH, Wise RP: Dual neuromuscular block in man. Anesthesiology 21:144–149, 1960
35. Lee C: Succinylcholine: its past, present, and future. Sem Anesth 3:293–302, 1984
36. Sprague DH, Mandel SD: Paroxysmal supraventricular tachycardia during anesthesia. Anesthesiology 46:75–77, 1977
37. Fogdall RP, Miller RD: Neuromuscular effects of enflurane, alone and combined with *d*-tubocurarine, pancuronium, and succinylcholine, in man. Anesthesiology 42:173–178, 1975
38. Miller RD, Eger EI, Way WL, et al: Comparative neuromuscular effects of Forane and halothane alone and in combination with d-tubocurarine in man. Anesthesiology 35:38–42, 1971a
39. Waud BE: Decrease in dose requirement of d-tubocurarine by volatile anesthetics. Anesthesiology 51:298–302, 1979
40. Miller RD, Way WL, Dolan WM, et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509–514, 1971b
41. Matsubara K, Kagawa M, Fukui Y.: *In vivo* and *in vitro* studies on cocaine metabolism: ecgonine methyl ester as a major metabolite of cocaine. Forens Sci Int 26:169–180, 1984
42. Kalow W, Britt BA, Chan FY: Epidemiology and inheritance of malignant hyperthermia. Int Anesthesiol Clin 17(4):119–139, 1979
43. Steward DJ: Malignant hyperthermia: the acute crisis. Int Anesthesiol Clin 17(4):1–9, 1979
44. Mobley B: Soman and the Ca^{2+}-pump activity of sarcoplasmic reticulum. Tech Summary DAMD17-84-C-4104, Annual Report, March 1984 to March 1985
45. Viby-Mogensen J: Interaction of other drugs with muscle relaxants. Semin Anesthesiol 4:52–64, 1985
46. Wade CE, Waring PP, Trail DS, et al: Acetylcholinesterase activity of plasma and erythrocytes during hemorrhage in conscious swine. LAIR Inst Report #229, Jan 1987a
47. Wade CE, Waring PP, Trail DS, et al: A multiple dose study of oral pyridostigmine in swine. LAIR Lab Note #87-67, March 1987b
48. Wade CE, Waring PP, Trail DS, et al: Effects of acute acetylcholinesterase inhibition by pyridostigmine bromide injection in euvolemic and hypovolemic conscious swine. LAIR Inst Report #235, April 1987c
49. Wade CE, Waring PP, Trail DS, et al: Effects of atropine, 2-PAM, or pyridostigmine in euvolemic or hemorrhagic conscious swine. LAIR Inst. Report #233, April 1987d
50. Levitzki A: Bacterial adaptation, visual adaptation, receptor desensitization—a common link? Trends Pharmacol Sci 7:3–6, 1986
51. Costa LG, Schwab BW, Murphy SD: Tolerance to anticholinesterase compounds in mammals. Toxicology 25:79–97, 1982
52. Pascuzzo GJ, Akaike A, Maleque MA, et al: The nature of the interactions of pyridostigmine with the nicotinic acetylcholine receptor-ionic channel complex. I. Agonist, desensitizing, and binding properties. Mol Pharmacol 25:92–101, 1984
53. Adler M, Maxwell D, Foster RE: *In vivo* and *in vitro* pathophysiology of mammalian skeletal muscle following acute and subacute exposure to pyridostigmine. Studies on muscle contractility and cellular mechanisms. In: Proc. IV Annu. Chemical Defense Bioscience Review, Aberdeen Proving Ground, MD, 1984, pp 173–192
54. Anderson RJ, Chamberlain, WL, Roesner, M, et al: Decreased tetanic contracture of rat skeletal muscle induced by pyridostigmine. J Toxicol Environ Health 18:221–230, 1986
55. Kunjappan VE, Brown EM, Alexander GD: Rapid sequence induction using vecuronium. Anesth Analg 65:503–506, 1986
56. Taboada JA, Rupp SM, Miller RD: Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology 64:243–247, 1986